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RESEARCH ARTICLE

Subacute aphasia recovery is associated with resting-state connectivity within and beyond the language network

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Abstract

Objective: To examine changes to connectivity after aphasia treatment in the first 3 months after stroke. **Methods**: Twenty people experiencing aphasia within the first 3 months of stroke completed MRI before and immediately following 15 hours of language treatment. They were classified based on their response to treatment on a naming test of nouns as either high responders (10% improvement or more), or low responders (<10% improvement). Groups were similar in age, gender distribution, education, days since stroke, stroke volume, and baseline severity. Resting-state functional connectivity analysis was limited to the connectivity of the left fusiform gyrus with the bilateral inferior frontal gyrus, supramarginal gyrus, angular gyrus, and superior, middle, and inferior temporal gyrus, based on previous studies showing the importance of left fusiform gyrus in naming performance. **Results**: Baseline ipsilateral connectivity between the left fusiform gyrus and the language network was similar between high and low responders to therapy when controlling for stroke volume. Following therapy, change in connectivity was significantly greater among high responders between the left fusiform gyrus and the ipsilateral and contralateral pars triangularis, ipsilateral pars opercularis and superior temporal gyrus, and contralateral angular gyrus when compared with low responders. **Interpretation**: An account of these findings incorporates primarily proximal connectivity restoration, but also potentially reflects select contralateral compensatory reorganization. The latter is often associated with chronic recovery, reflecting the transitional nature of the subacute period.

Introduction

Aphasia commonly occurs following stroke involving left-dominant structures that underpin the brain's language network[1,2] and persists to some degree in over half of all who experience it initially.[3] Speech and language therapy (SLT) is the mainstay treatment[4,5] and is considered beneficial for recovery.[6,7] Resting-state functional MRI (rsfMRI) can be used to indirectly examine the fidelity of relationships among interconnected regions within the language network and provide insights into the structural underpinnings of recovery. More specifically, resting-state functional connectivity (rsFC) can provide insight into the neurological differences between patients who respond to treatment and recover well and those who do not. A recent review by Cassidy et al.[8] drew together diverse lines of evidence to support the notion that changes in rsFC are, in fact, *causal* of recovery in the context of stroke rehabilitation.

The language network typically includes the left inferior frontal gyrus (IFG), supramarginal gyrus (SMG), angular gyrus (AG), temporal gyri (superior, STG; medial, MTG; and inferior, ITG), and the fusiform gyrus (FuG).[9,10] The fusiform gyrus appears to fulfill a role uniquely critical to naming, integrating lexical retrieval with semantic

content.[11,12] Prior studies have demonstrated the impact of lesions resulting in aphasia on language network connectivity,[13,14] and have begun to appreciate the impacts of treatment.[15] In a recent scoping review, Klingbeil et al.[16] identified four rsfMRI studies of aphasia treatment that examined rsFC change in a total of 39 patients.[17–20] No single study had considered more than a dozen patients, and all four were conducted in the chronic phase (a minimum of 7 months after stroke). To our knowledge, no prior investigation has examined changes to functional connectivity before and after aphasia treatment in the acute–subacute period, despite the frequent observation that this is the period when the most profound recovery occurs and the most rehabilitation is provided. As the treatment in our trial focused on lexical retrieval, we centered our investigation into connectivity on the left FuG.

In this exploratory investigation, we utilized pre- and post-treatment rsfMRI gathered during a recent clinical trial[21] to examine two questions: (1) Do individuals who ultimately show more recovery of naming following treatment have higher baseline functional connectivity between the left FuG and other ipsilateral structures in the language network? and (2) Do individuals who show greater recovery of naming following treatment demonstrate significantly greater *change in* functional connectivity between the left FuG and *either* left-lateralized structures important for language or their contralateral homologs after treatment? We suspected that individuals who responded well to lexical therapy may have higher baseline functional connectivity to the left FuG and that their greater extent of recovery would be associated with increased connectivity between this region and others within the language network.

Methods

Participants

Twenty participants were identified from a recently completed clinical trial of neurostimulation-supported language treatment for acute–subacute poststroke aphasia[21] on the basis of having been eligible for and completed rsfMRI. In the clinical trial, 92 patients were screened and 58 were randomized. All participants were right-handed native English speakers <3 months of acute ischemic left hemisphere stroke diagnosed with aphasia by the Western Aphasia Battery-Revised (WAB-R),[22] with no history of co-occurring neurological diagnoses affecting the brain and normal or corrected-to-normal vision and hearing. All procedures were approved by the Johns Hopkins Medicine Institutional Review Board (IRB00089018). The study was registered with ClinicalTrials.gov (NCT02674490).

Behavioral assessment and procedures

All participants had received an NIH Stroke Scale[23] (NIHSS, a measure of overall stroke severity) acutely and completed the 175-item Philadelphia Naming Test[24] (PNT) both immediately following consent at baseline and 1-week following treatment. Treatment provided during the trial consisted of 15 h of speech-language pathologist-supervised computer-delivered language treatment over 3–5 weeks, over and above any clinically indicated rehabilitation. Treatment consisted of a picture-verification task. For each item, patients saw a picture, then a video of a person saying either the name of the picture or a semantic or phonological foil. They responded by identifying when the picture and name matched (pressing a green button) or did not match (pressing a red button) and received immediate item-level feedback (via a smiling or frowning face) as well as session accuracy feedback. This task requires the patient to latently access a label of the picture presented (that is, to think of the label without producing the word) to determine whether the spoken label is consistent or inconsistent with that internal representation. The therapy task has been used to support change in naming accuracy measured on the PNT in a parallel trial in the chronic phase, regardless of neurostimulation.[25]

Patients were binned on the basis of naming improvement following therapy with those who improved by at least 10% accuracy (17 items) grouped as "high responders" and those who improved by less than 10% accuracy ("low responders"). An improvement of 5% on the WAB or other common assessments of language previously has been identified as a benchmark of significant change.[26] Thus, in arriving at an appropriate operationalization of *high* response to treatment, we chose to double this standard. No participant in this sub-study performed worse in naming after treatment.

Imaging

Participants who consented to rsfMRI received this imaging at two timepoints – directly before and 1 week after treatment. Acquisition parameters mirrored those previously reported on in Faria and colleagures.[27] Patients were scanned using a 3 Tesla MR scanner (Achieva, Philips Healthcare, Best, The Netherlands). Anatomical images were acquired using a 3D MPRAGE sequence with a $1.0 \times 1.0 \times 1.2$ mm^3 resolution. rsfMRI scans were acquired using a 2D EPI sequence with fat suppression and SENSE partially parallel image acceleration to obtain a 3×3 mm (80 by 80 voxels) in-plane resolution in thirty-seven 3 mm transverse slices with a 1 mm slice gap. The rsfMRI scans were "postprocessed" in a

web-based public service (MRICloud), following common steps that include slice-time-correction, realignment to the mean frame and motion correction, outlier frame detection and rejection, and physiological nuisance correction. The anatomical images, automatically segmented in 283 regions of interest (ROIs), were coregistered to the respective rsfMRI, together with the parcellation maps. The rsfMRI time courses of 76 cortical regions were extracted, from which the correlations (and Fisher's Z-transformed correlations) were calculated. All of these steps of image processing are further detailed in our previous publication.[27] In this study, we focused on ROIs identified as part of the language network: bilateral FuG, IFG, SMG, AG, STG, MTG, and ITG.

Statistical analysis

To answer Question One, baseline correlations between ipsilateral ROIs were calculated between the left FuG and pars opercularis, pars orbitalis, pars triangularis (IFG), SMG, AG, STG, MTG., and ITG. To answer Question Two, the change to correlations between ROIs was calculated considering both ipsilateral and contralateral connections with the left FuG resulting in 17 pairings of 9 regions. All correlations were Z-transformed prior to analysis. Multivariable analyses of variance were used in which Z-transformed correlations or changes in correlations were entered together as dependent variables, PNT responder group was entered as a fixed factor, and stroke volume was entered as a covariate ($\alpha = 0.05$).

Results

Do high responders have higher baseline connectivity among language regions than low responders?

Twenty patients completed baseline functional MRI (9 high responders and 11 low responders). Groups were statistically similar in age, gender distribution, education, days since stroke, stroke volume, proportion of damage to regions of interest within the language network, baseline stroke severity on the NIHSS, and overall aphasia severity on the WAB-R and PNT (Table 1). Proportion of damage to regions of interest correlated with baseline connectivity to the left FuG in groups considered together driven by relationships between proportions of regions lesioned and connectivity among low responders. No significant correlations were observed among high responders. However, no proportion of damage was correlated significantly with connectivity between the left FuG and *that region* in any instance considered (e.g., percentage of pars opercularis lesioned correlated with the connectivity between the right SMG and left FuG, but not between the pars opercularis and the left FuG). These relationships are illustrated in Figure 1. Directly before treatment (baseline), there were no significant differences between high and low responders in connectivity between language regions (Table 2).

Table 1. Sample characteristics.

	High responders	Low responders
N	9	11
Age	67 ± 13; [47–84]	73 ± 8; [61–86]
M:F	7:2	4:7
Education (years)	17 ± 2; [12–20]	14 ± 3; [12–20]
Days since stroke	42 ± 28; [9–97]	59 ± 26; [14–94]
Stroke volume (cc)	62 ± 60; [2–181]	51 ± 45; [1–125]
Pars opercularis (%)	18 ± 32; [0–99]	9 ± 25; [0–82]
Pars orbitalis (%)	17 ± 33; [0–87]	0 ± 0; [0–0.1]
Pars triangularis (%)	17 ± 34; [0–99]	2 ± 7; [0–22]
Supramarginal gyrus (%)	10 ± 21; [0–60]	23 ± 30; [0–85]
Angular gyrus (%)	4 ± 8; [0–24]	27 ± 37; [0–85]
Superior temporal gyrus (%)	15 ± 21; [0–44]	14 ± 21; [0–57]
Middle temporal gyrus (%)	12 ± 18; [0–49]	10 ± 15; [0–39]
Inferior temporal gyrus (%)	3 ± 8; [0–25]	3 ± 7; [0–21]
Fusiform gyrus (%)	0 ± 1; [0–1]	2 ± 5; [0–17]
Baseline NIHSS	3 ± 2; [2–7]	4 ± 2; [1–9]
Aphasia severity (/100)	59 ± 21; [27–87]	70 ± 24; [16–93]
Anomic	3	5
Broca's	2	3
Conduction	0	1
Global	1	0
Transcortical motor	1	1
Transcortical sensory	1	0
Wernicke's	1	1
PNT baseline	78 ± 38; [29.5–136]	99 ± 65; [0–161.5]
PNT improvement	38 ± 10; [29–56.5]	8 ± 3; [4–14]

Reported as mean ± standard deviation and range unless otherwise noted. Stroke volume is noted as well as percent of each left region of interest where lesion was present. NIHSS, a measure of overall stroke severity. Aphasia severity was measured using the Western Aphasia Battery-Revised Aphasia Quotient. Subtype counts also are provided. Days since stroke refers to the number of days between the stroke and the baseline assessment.
NIHSS, NIH Stroke Scale; PNT, Philadelphia Naming Test.

Do high responders demonstrate greater change in functional connectivity than low responders?

Nineteen patients completed testing and imaging both at baseline and immediately following language treatment

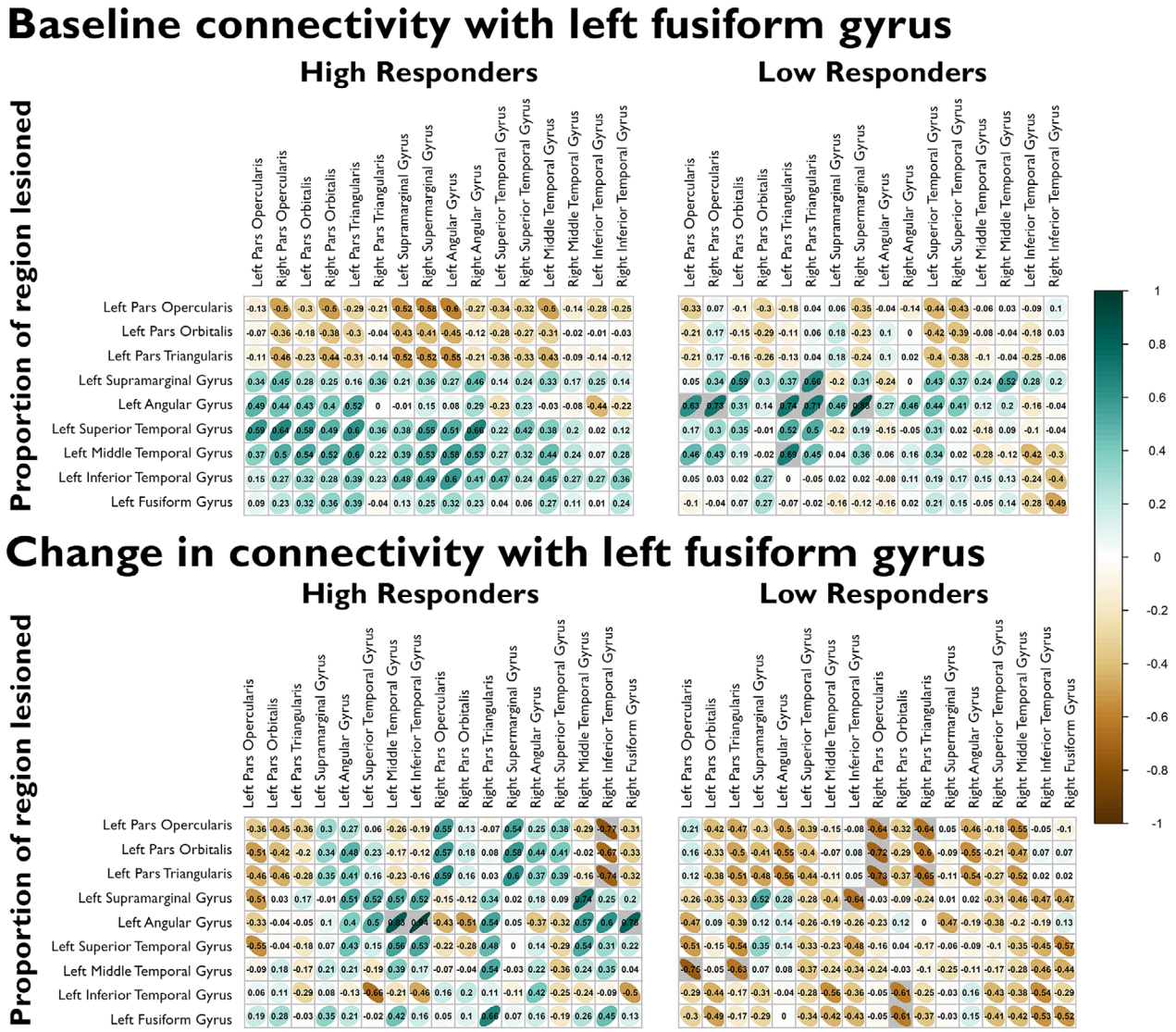

Figure 1. Correlations between lesion and connectivity to left fusiform gyrus by group. Pearson correlations between the proportion of each region of interest affected by lesion (row) and the connectivity of regions and their right hemisphere homologs to the left fusiform (column) are included in each correlogram. Each cell contains the correlation value and an ellipse illustrating the strength and direction of the correlation. Significant correlations ($p < 0.05$) are shaded in gray. There was no evidence of correlation between proportion of region lesioned and connectivity to that region at baseline or after treatment. However, while relationship trends were similar between high and low responders at baseline, the figure highlights the striking difference between groups after therapy. Among high responders, the majority of correlations between lesioned regions in the language network and change in connectivity to the left fusiform are positive. Among low responders, these relationships are almost exclusively negative, and many of them are significant.

(one high responder declined repeated imaging). Groups remained similar across all demographic and stroke characteristics reported in Table 1. Proportion of damage to regions of interest correlated with changes in connectivity to the left FuG in groups considered together, and among high and low responders separately. No significant correlations were observed between lesioned region and connectivity to that region across groups or in either group considered separately. These relationships are illustrated in Figure 1. Following treatment, high responders showed greater than average increases in connectivity between the left FuG and other language structures in nearly all instances; low responders showed the opposite trend (see Fig. 2 for change in individual connectivity). Significant differences in connectivity between high responders and low responders were noted between the left FuG and the

Table 2. Pretreatment ipsilateral connectivity between key ipsilateral language regions and the left fusiform gyrus.

	High responders	Low responders
Pars orbitalis	0.38 ± 0.29	0.25 ± 0.21
Pars triangularis	0.28 ± 0.29	0.25 ± 0.31
Pars opercularis	0.32 ± 0.33	0.22 ± 0.27
SMG	0.29 ± 0.42	0.20 ± 0.28
AG	0.24 ± 0.36	0.19 ± 0.28
STG	0.43 ± 0.43	0.48 ± 0.21
MTG	0.65 ± 0.29	0.66 ± 0.32
ITG	0.97 ± 0.36	0.86 ± 0.25

Reported as mean ± standard deviation.

ipsilateral pars opercularis, pars triangularis, and superior temporal gyrus. Significant differences also were noted in the connectivity between the left FuG and the contralateral pars triangularis and angular gyrus (Table 3).

Discussion

In this investigation, we sought to examine two questions important to understanding the relationship between connectivity in the language network and response to post-stroke aphasia treatment. Contrasting individuals who responded relatively well to lexical treatment with those who showed a negligible response, we first examined whether the groups differed in baseline connectivity between a critical region for lexical retrieval, the left FuG, and ipsilateral structures within the language network. Second, we examined whether changes in connectivity between the left FuG and these same structures, as well as their contralateral homologs, from before treatment to after treatment differed among those who responded well and those who did not. Prior to answering either question regarding connectivity, we were surprised first to find that in our sample, individuals who recovered naming better were similar to those who recovered naming more poorly

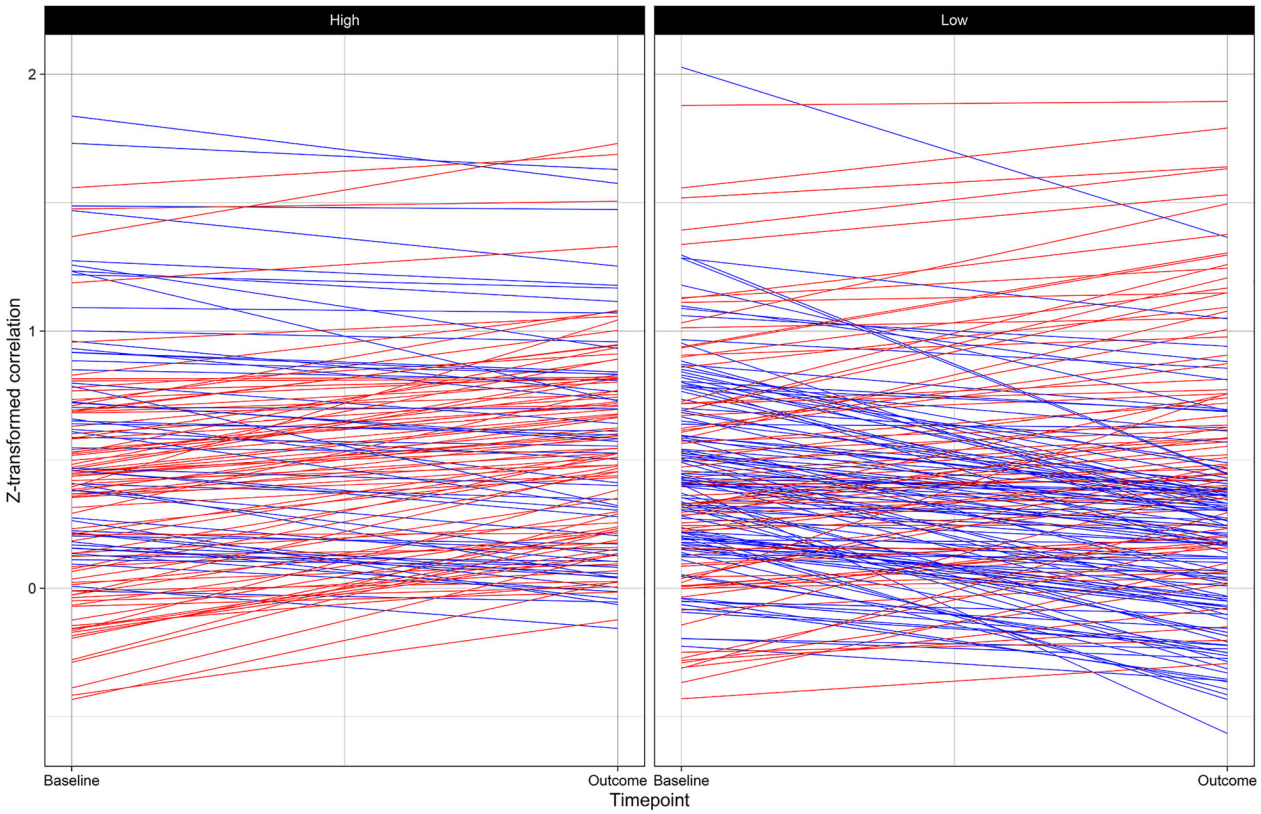

Figure 2. Summary of individual changes in connectivity to left fusiform gyrus. High responders showed an increase in average connectivity to the left fusiform gyrus across ipsilateral regions in the language network and contralateral homologs from baseline to the outcome measure following treatment. Low responders showed a decrease in connectivity over this period. This figure is a plot of Z-transformed correlations for each region pair from each individual at baseline and following treatment in order to demonstrate the tendency of constituent data to mirror the observed central tendency. Increased connectivity is represented in red and decreased connectivity is represented in blue. Among high responders, 62% of connections increased, while only 41% of connections among low responders increased.

Table 3. Change in connectivity between key language regions and the left fusiform gyrus.

	Ipsilateral (left)			Contralateral (right)		
	High responders	Low responders	η_p^2	High responders	Low responders	η_p^2
Pars orbitalis	0.12 ± 0.23	−0.003 ± 0.23		0.06 ± 0.19	−0.04 ± 0.33	
Pars triangularis	0.15 ± 0.26	−0.15 ± 0.21	0.46**	0.09 ± 0.15	−0.23 ± 0.22	0.41**
Pars opercularis	0.18 ± 0.25	−0.08 ± 0.21	0.38**	0.14 ± 0.19	−0.15 ± 0.38	
SMG	0.20 ± 0.24	−0.10 ± 0.35		0.11 ± 0.25	−0.14 ± 0.32	
AG	0.09 ± 0.27	−0.07 ± 0.24		0.15 ± 0.26	−0.16 ± 0.28	0.23*
STG	0.16 ± 0.22	−0.23 ± 0.35	0.35**	0.09 ± 0.20	−0.06 ± 0.37	
MTG	0.04 ± 0.15	−0.11 ± 0.42		0.07 ± 0.13	0.02 ± 0.43	
ITG	−0.11 ± 0.34	−0.04 ± 0.37		−0.05 ± 0.22	0.002 ± 0.31	
FuG	–			−0.02 ± 0.20	−0.02 ± 0.29	

Reported as mean ± standard deviation. Effect sizes reported for significant contrasts only.
*$p < 0.05$;
**$p \leq 0.01$.

following treatment. Not only were the groups similar in personal risk factors often associated with poorer stroke outcomes, such as age, they were similar in stroke-specific factors like lesion size, overall severity on the NIHSS, and baseline aphasia severity on the WAB-R. It is possible that these frequently reported effects, which did trend in the expected direction, simply were not significant due to small sample size.

We initially suspected that individuals who responded well to lexical therapy may have higher baseline functional connectivity between the left FuG and regions within the language network. However, we found that high and low responders were similar in their acute–subacute baseline ipsilateral connectivity within the language network when controlling for lesion size. This is inconsistent with prior work examining predictors of treatment in the chronic phase,[28] wherein greater gains following semantic feature naming therapy have been associated with greater baseline language network connectivity. This may reflect an important difference between the physiological underpinnings of chronic versus acute–subacute recovery. The acute–subacute period is characterized by spontaneous recovery predominantly via reactive neuroplasticity (neural migration, neurogenesis, axonal growth, remyelination, dendritic spine expansion, synaptogenesis)[29] supported by experience-dependent neuroplasticity,[30] which may not yet differ much between high and low responders. In contrast, chronic recovery relies heavily on ipsilateral *and* contralateral reorganization and compensation, which may differ between high and low responders.[31] This unexpected result warrants replication in a larger sample.

When examining our second question, we anticipated that individuals who responded well to therapy would show greater improvements in connectivity between the left FuG and the language network, as well as contralateral homologs. This hypothesis is consistent with the account that restored connectivity is the direct cause of aphasia recovery.[8] As anticipated, numerous differences in connectivity differentiated those who responded well to therapy and those who did not. High responders showed increased connectivity between the left FuG and language network regions and contralateral homologs in nearly every pairing examined. Low responders meanwhile showed decreases in connectivity within both the language network and contralateral structures following treatment. Differences between high and low responders in changes to connectivity reached significance for connectivity between the left FuG and the left pars triangularis, pars opercularis, and STG and the right pars triangularis and AG. The pars triangularis and pars opercularis together make up the area of the IFG known as Broca's area, which is essential to speech production. The STG is thought to serve as the auditory association cortex within the Hickok-Poeppel model of language.[10] In this model, the right AG has been associated with visuospatial attention toward salient features and is thought to mediate memory retrieval. Among low responders, smaller changes in connectivity with the left FuG also were consistently associated with greater proportions of lesion to other structures within the language network. Thus, an account of these findings incorporates primarily proximal connectivity restoration, but also potentially reflects select contralateral compensatory reorganization, more closely associated with chronic recovery.

This investigation is limited by the small sample size and the necessity to consider numerous contrasts relevant to the two investigative questions. While our sample size in the present exploration is larger than the majority of those reported in the chronic literature on this topic, variability in the acute–subacute phase also is greater. Given the uncommon nature of inquiries into aphasia in the acute–subacute period, we chose to approach these

exploratory questions by adopting a relatively liberal approach to study-wide error. We acknowledge that these findings must be replicated in larger and more sophisticated designs prior to generating firm conclusions regarding their interpretation. Moreover, we are limited in our ability to answer finer-grain questions about the interacting influences of various individual factors, such as aphasia type, lesion location, sex, or age. Nevertheless, the differences observed here provide a valuable first look that justifies future investigations into how the relationship between connectivity and response to therapy may differ across stages of poststroke recovery.

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Author Contributions

AEH conceived of the study. MDS and AVF acquired and analyzed the data. Interpretation was supported by CR, LB, and JF. MDS and AVF drafted the manuscript. All authors examined and approved the final draft.

Conflict of Interest

Dr. Hillis receives compensation from the American Heart Association as Editor-in-Chief of Stroke and from Elsevier as Associate Editor of PracticeUpdate Neurology. All authors receive salary support from NIH (NIDCD) through grants. The authors report no additional competing interests.

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Data Availability Statement

Anonymized data will be made available upon request to the authors, subject to review by the Johns Hopkins University School of Medicine Institutional Review Board resulting in a formal data-sharing agreement.

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